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Evaluation of the optimal duration of immunosuppressive treatment after induction of remission, in patients with ANCA vasculitis

Submission date	Recruitment status	[_] Prospectively registered
04/01/2017	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
10/01/2017	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
30/05/2017	Circulatory System	

Plain English summary of protocol

Background and study aims

Vasculitis is a condition in which the immune system attacks blood vessels by mistake, leading them to lead fluid into tissues causing inflammation (swelling). This happens because antibodies, which are normally produced by the immune system to fight germs, start attacking a type of white blood cell called neutrophils. In the case of ANCA vasculitis, the antibodies which are attacking the neutrophils are called Anti-Neutrophil Cytoplasmic Autoantibodies (ANCA). When ANCAs attack the neutorphils, the neutrophils in turn start to attack the walls of small blood vessels in different parts of the body. The treatment of ANCA vasculitis is by drugs which suppress the immune system (immunosuppressive drugs). These drugs, which include steroids, have side-effects and it is desirable to reduce the doses and stop them where possible. However vasculitis can return when the drugs are reduced or stopped. The aim of this study is to investigate how long immunosuppressive drugs should be given to patients with vasculitis.

Who can participate?

Adults with ANCA vasculitis which has been treated and is now under good control.

What does the study involve?

Participants are randomly allocated to one of two groups. In both groups, before they are allocated to the different groups, participants are taking immunosuppressive therapy, which involves taking the drug azathioprine and prednisolone every day by mouth for three months. Those in the first group then stop taking the azathioprine and lower the dose of prednisolone, which is stopped altogether by five months later. Those in the second group continue to take their azathioprine until the end of the study (30 months) and gradually reduce and eventually stop taking their prednisolone between 18 and 24 months. At the start of the study and then every three months until the end of the study (30 months), participants attend visits where they have blood samples taken to find out whether the vasculitis has come back and to assess their health.

What are the possible benefits and risks of participating?

Not provided at time of registration

Where is the study run from?
1. Addenbrooke's Hospital (UK)
2. Hôpital Cochin (France)
3. Maastricht University (Netherlands)
4. Universitetssjukhuset Linköping (Sweden)
5. Uniklinikum Aachen (Germany)
6. Provicial Barcelona Hospital Hospital Clínic de Barcelona (Spain)

When is the study starting and how long is it expected to run for?
January 1994 to September 2012

Who is funding the study?
European Community (EC) BIOMED-1 Concerted Action Programme (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
1

Study information

Scientific Title

Randomised controlled trial comparing relapse rate between standard (18 to 24 months) and prolonged (48 months) immunosuppression with azathioprine and prednisolone, in patients in the remission phase of ANCA vasculitis

Acronym
REMAIN

Study objectives
Prolonged maintenance therapy with low-dose prednisolone and azathioprine reduces long-term morbidity in systemic vasculitis, by reducing the frequency of relapse, when compared with cessation of therapy in the second year, as suggested by current guidelines.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NHS Executive North West MREC, 07/03/2001, ref: MREC/00/8/74

Primary study design
Interventional

Study design
Prospective open-label randomised controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
ANCA-associated vasculitis

Interventions
Patients with ANCA vasculitis in stable remission are included 18 to 24 months after initiation of immunosuppressive therapy. Patients are randomised in a 1:1 ratio to either withdraw from immunosupprssion (Group W) or continue immunosuppression (Group C). Prior to randomisation, immunosuppressive therapy involves oral azathioprine at a daily dose of 1 mg/kg and oral prednisolone at the dose of 7.5 mg/day.

Group W: Participants receive oral azathioprine at the dose of 0.75 mg/kg for 3 months and then stop this drug. In addition, prednisolone is tapered to 5 mg/day at randomisation and then progressively stopped before month 5.

Group C: Participants continue oral azathioprine at the daily dose of 1 mg/kg for 30 months, until end of study. In addition, oral prednisolone is tapered to 5 mg/day at month 3, and then continued until month 18. After month 18, prednisolone is progressively stopped, before reaching month 24.

Duration of follow-up for both arms will be 30 months, with evaluation (examination and blood tests) every 3 months.

Intervention Type

Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
1. Azathioprine 2. Prednisolone

Primary outcome(s)
Rate of vasculitis relapse is measured using the Birmingham Vasculitis Activity Score (BVAS) continuously from baseline to 30 months.

Key secondary outcome(s)
1. Incidence of major and minor relapse is measured using the Birmingham Vasculitis Activity Score (BVAS) continuously from baseline to 30 months
2. Mortality rate is measured continuously from baseline to 30 months
3. Adverse events of therapy are observed continuously from baseline to 30 months
4. Cumulative damage is assessed using the Vasculitis Damage Index (VDI) from baseline to 30 months
5. Renal function is assessed by measuring estimated Glomerular Filtration Rate (eGFR) from baseline to 30 months
6. Incidence of end-stage renal disease (ESRD) is monitored from baseline to 30 months
7. ANCA status

Completion date
01/09/2012

Eligibility

Key inclusion criteria
1. Diagnosis of MPA, GPA or renal-limited vasculitis
2. Renal involvement and/or other threatened loss of function of a vital organ (lung, brain, eye, motor nerve, or gut); and ANCA positivity (ANCA-negative patients were eligible for enrollment in the study only when there was histologic confirmation of pauci-immune vasculitis)
3. Remission-induction therapy with cyclophosphamide and prednisolone for at least 3 months, with or without plasma exchanges
4. Stable remission on azathioprine/prednisolone
5. Aged 18 years and over

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Age under 18 years
2. Pregnancy
3. Previous malignancy
4. Known HIV infection
5. Previous life-threatening relapse
6. End-stage renal disease (ESRD) at inclusion and allergy to study medications. Patients not in stable remission for at least six months at 18 months after commencement of therapy and patients who had discontinued azathioprine and/or prednisolone are excluded from the study.

Date of first enrolment
01/09/1998

Date of final enrolment
01/03/2010

Locations

Countries of recruitment
United Kingdom

England

Czech Republic

Finland

France

Germany

Italy

Lithuania

Netherlands

Spain

Sweden

Switzerland

Study participating centre
Addenbrooke's Hospital
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Sponsor information

Organisation
European Vasculitis Society

Funder(s)

Funder type
Research organisation

Funder Name
European Community (EC) BIOMED-1 Concerted Action Programme

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Alexandre Karras (akarras3@gmail.com) or David Jayne (dj106@cam.ac.uk)

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/10/2017		Yes	No